#181
3/31/03

b.) Amendments to the Claims

1. (Currently Amended) A cyclic peptide, or a pharmaceutically acceptable salt thereof, having an activity to restore DNA-binding activity or P53 protein-dependent transcription activity to mutant P53 protein, said peptide being represented by formula (I):

$R^1(X^1)^{n1}(X^2)^{n2}(X^3)^{n3}(X^4)^{n4}(X^5)^{n5}(X^6)^{n6}(X^7)^{n7}(X^8)^{n8}(X^9)^{n9}(X^{10})^{n10}(X^{11})^{n11}(X^{12})^{n12}$

$(X^{13})^{n13}(X^{14})^{n14}(X^{15})^{n15}(X^{16})^{n16}(X^{17})^{n17}R^2$ (I)

wherein

any of X^1 to X^{17} may be denoted by X^i, i being an integer of 1 to 17;

any of n1 to n17 may be denoted by ni, where ni represents 0 or 1 such that $(X^i)^{ni}$ represents X^i when ni is 1 and represents a bond when ni is 0;

ni represents 1 for at least 7 different X^is, with R^1 bonded to the N-terminus and R^2 bonded to the C-terminus:

any of X^1 to X^{11} where ni represents 1 may be denoted by X^p and any of X^8 to X^{17} where ni represents 1 may be denoted by X^q such that $q > p$; ~~to represent one sequence, in which a functional group in residue X^p (where p is an integer of 1 to 11) and a functional group in residue X^q (where q is an integer of 8 to 17, provided that q is larger than p) together form a cyclic structure;~~

R^1 represents substituted or unsubstituted alkanoyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted aralkyloxycarbonyl, substituted or unsubstituted aryloxycarbonyl, substituted or unsubstituted aroyl, 9-fluorenylmethoxycarbonyl or hydrogen;

R^2 represents substituted or unsubstituted alkoxy, substituted or

unsubstituted aralkyloxy, amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted aralkylamino, substituted or unsubstituted arylamino or hydroxy;

R^1 and R^2 may together form a single bond when the total number of amino acid and organic acid residues having an SH group in the peptide is two or less , or a functional group in X^p and a functional group in X^q may together form a covalent bond to form a cyclic structure together with any intervening X^i residues;

X^1 represents a residue of 2-mercaptobenzoic acid, 3-mercaptopropionic acid, 4-mercaptobutanoic acid, mercaptoacetic acid, adipic acid, suberic acid, cysteine, homocysteine, penicillamine, aspartic acid, glutamic acid, homoglutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid, ornithine, lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine, serine, threonine, homoserine, α-methylserine, 3-hydroxyproline or 4-hydroxyproline;

X^2 represents a residue of leucine, isoleucine, valine, alanine, norvaline, norleucine, 2-aminobutanoic acid, homoleucine, β-alanine, α-aminoisobutanoic acid, β-cyclopropylalanine, β-chloroalanine, 1-aminocyclopentane-1-carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, 2-amino-1-cyclopentanecarboxylic acid, t-butylglycine, diethylglycine, t-butylalanine, O-methylserine, cyclohexylglycine, cyclohexylalanine or glycine;

X^3 represents a residue of lysine arginine, ornithine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine or glycine;

X^4 represents a residue of serine, threonine, homoserine, α-

methylserine, 3-hydroxyproline, 4-hydroxyproline, cysteine, homocysteine, penicillamine, aspartic acid, glutamic acid, homoglutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid, ornithine, lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine, glycine, 2-mercaptobenzoic acid, 3-mercaptopropionic acid, 4-mercaptobutanoic acid, mercaptoacetic acid, adipic acid or suberic acid;

X^5 represents a residue of lysine, arginine, ornithine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine or glycine;

X^6 represents a residue of lysine, arginine, ornithine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine or glycine;

X^7 represents a residue of alanine, β-alanine, 2-aminobenzoic acid, 3-aminobenzoic acid, 4-aminobenzoic acid, 3-aminomethylbenzoic acid, proline, 3-hydroxyproline, 4-hydroxyproline, L-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid, cysteine, homocysteine, penicillamine, 2,3-diaminopropionic acid, 2,4-diaminobutanoic acid, ornithine, lysine, p-aminophenylalanine, aspartic acid, glutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid or glycine;

X^8 represents a residue of glutamine, asparagine, cysteine, homocysteine, penicillamine, aspartic acid, glutamic acid, homoglutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid, ornithine, lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine, serine, threonine, homoserine, α-methylserine, 3-hydroxyproline, 4-hydroxyproline, glycine, 2-mercaptobenzoic acid, 3-mercaptopropionic acid, 4-mercaptobutanoic acid, mercaptoacetic

acid, adipic acid or suberic acid;

X^9 represents a residue of serine, threonine, homoserine, α-methylserine, 3-hydroxyproline, 4-hydroxyproline, cysteine, homocysteine, penicillamine, aspartic acid, glutamic acid, homoglutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid, ornithine, lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine, glycine, 2-mercaptobenzoic acid, 3-mercaptopropionic acid, 4-mercaptobutanoic acid, mercaptoacetic acid, adipic acid or suberic acid;

X^{10} represents a residue of serine, threonine, homoserine, α-methylserine, hydroxyproline, cysteine, homocysteine, penicillamine, aspartic acid, glutamic acid, homoglutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid, ornithine, lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine, glycine, 2-mercaptobenzoic acid, 3-mercaptopropionic acid, 4-mercaptobutanoic acid, mercaptoacetic acid, adipic acid or suberic acid;

X^{11} represents a residue of serine, threonine, homoserine, α-methylserine, hydroxyproline, cysteine, homocysteine, penicillamine, aspartic acid, glutamic acid, homoglutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid, ornithine, lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine, glycine, 2-mercaptobenzoic acid, 3-mercaptopropionic acid, 4-mercaptobutanoic acid, mercaptoacetic acid, adipic acid or suberic acid;

X^{12} represents a residue of lysine, arginine, ornithine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine or glycine;

X^{13} represents a residue of histidine, alanine, 4-thiazolylalanine, 2-thienylalanine, 2-pyridylalanine, 3-pyridylalanine, 4-pyridylalanine, (3-N-methyl)piperidylalanine, 3-(2-quinoyl)alanine, serine, threonine, homoserine, α-methylserine, 3-hydroxyproline, 4-hydroxyproline, cysteine, homocysteine, penicillamine, aspartic acid, glutamic acid, homoglutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid, ornithine, lysine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine or glycine;

X^{14} represents a residue of lysine, arginine, ornithine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine, serine, threonine, homoserine, α-methylserine, 3-hydroxyproline, 4-hydroxyproline, cysteine, homocysteine, penicillamine, aspartic acid, glutamic acid, homoglutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid or glycine, and an amino group or guanidino group in the side chain of X^{14} may be modified with R^3 (where R^3 is independently selected from the moieties of R^1;

X^{15} represents lysine, arginine, ornithine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid, p-aminophenylalanine or glycine;

X^{16} represents a residue of leucine, alanine, 4-thiazolylalanine, 2-thienylalanine, isoleucine, norleucine, homoleucine, valine, norvaline, β-alanine, α-aminoisobutanoic acid, 2-aminobutanoic acid, β-cyclopropylalanine, β-chloroalanine, 1-aminocyclopentane-1-carboxylic acid, 1-amino-l-cyclohexanecarboxylic acid, 2-amino-1-cyclopentanecarboxylic acid, t-butylglycine, diethylglycine, t-butylalanine, O-methylserine, cyclohexylglycine, cyclohexylalanine or glycine;

X^{17} represents a residue of 2-mercaptoaniline, cysteamine, homocysteamine, cysteine, homocysteine, penicillamine, ornithine, lysine, 2,3-diaminopropionic acid, 2,4-diaminobutanoic acid, p-aminophenylalanine, glutamic acid, aspartic acid, homoglutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid or 2-aminosuberic acid; ~~and~~

~~R^2 represents substituted or unsubstituted alkoxy, substituted or unsubstituted aralkyloxy, amino, substituted or unsubstituted alkylamino, substituted or unsubstituted dialkylamino, substituted or unsubstituted aralkylamino, substituted or unsubstituted arylamino or hydroxy;~~

where ~~organic acid or amino acid residues independently selected from X^1 to X^{17} may be deleted, substituted or added, or~~ a 12-aminododecanoic acid residues may be ~~substituted or~~ added at the N– or C- terminus of the petpide~~, provided that at least seven X^i's where ni=1 remain~~.

2. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 1, wherein said cyclic structure is formed by a S-S, S-CH_2-S, S-CH_2-C_6H_4-CH_2-S, S-CH_2-CO, CO-NH, NH-CO, O-CO or CO-O bond between X^p and X^q.

3. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 2, wherein X^p (np=1) is an N-terminal residue and X^q (nq=1) is a C-terminal residue.

4. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 2, wherein X^p (np=1) is not an N-terminal residue and X^q (nq=1) is not a C-terminal residue.

5. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 2, wherein X^p (np=1) is not an N-terminal residue and X^q (nq=1) is a C-terminal residue.

6. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 2, wherein X^p (np=1) is an N-terminal residue and X^q (nq=1) is not a C-terminal residue.

7. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 3, wherein X^p (np=1) is X^1 and X^q (nq=1) is X^{17}.

8. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 6, wherein X^p (np=1) is X^1 and X^q (nq=1) is X^{17}.

9. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 3, wherein X^p (np=1) is X^1 and X^q (nq=1) is X^{16}.

10. (Previously Amended) A peptide or a pharmaceutically acceptable salt

thereof according to claim 6, wherein X^p (np=1) is an N-terminal residue and X^q (nq=1) is X^8.

11. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 4, wherein X^p (np=1) is X^8 and X^q (nq=1) is X^{14}.

12. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 5, wherein X^p (np=1) is X^3 and X^q (nq=1) is a C-terminal residue.

13. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 4, wherein X^p (np=1) is X^3 and X^q (nq=1) is not a C-terminal residue.

14. (Previously Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 6, wherein X^p (np=1) is an N-terminal residue and X^q (nq=1) is X^{11}.

15. (Currently Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 1, said peptide having an amino acid sequence shown by one of SEQ ID NOS: 4-7 and 16-32 in which ~~one to several organic acid or amino acid residues independently selected from X^1 to X^{17} may be deleted, substituted or added, or~~ a 12-

aminododecanoic acid residues may be ~~substituted or~~ added at the – or C- terminus of the peptide.

16. (Currently Amended) A peptide or a pharmaceutically acceptable salt thereof according to claim 15, said peptide having an amino acid sequence shown by one of SEQ ID NOS: 4-7, 16, 19 and 25-32 in which ~~one to several organic acid or amino acid residues independently selected from X^1 to X^{17} may be deleted, substituted or added, or~~ a 12-aminododecanoic acid residues may be substituted or added at the – or C- terminus of the petpide.